D3

PATENT SPECIFICATION (11) 1415210

1415210

(21) Application No. 26557/73 (22) Filed 4 June 1973
(31) Convention Application No. 259469 (32) Filed 5 June 1972 in
(33) United States of America (US)
(44) Complete Specification published 26 Nov. 1975
(51) INT CL² B01D 13/00 A61K 9/00
(52) Index at acceptance
B1X 6BX 6D1 6D4 6DX 6F2 6F4 6FX 6HX 6L3
A5B 753 757 75Y

(19)

(54) OSMOTIC DISPENSER

(71) We, ALZA CORPORATION, a Corporation organized and existing under the laws of the State of California, United States of America, of 950 Page Mill Road, Palo Alto, County of Santa Clara, California, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to an osmotic device for dispensing a useful agent at a controlled rate.

Many useful agents such as drugs and agricultural chemicals, act with improved efficiency when they are delivered at controlled rates for prolonged periods of time. In the past, controlled rates of release of agent have been achieved primarily by restricting the agent within a coating or membrane which slowly erodes and releases the agent or by enclosing the agent in a membrane through which the agent can slowly diffuse.

Osmosis and osmotic pressure have also been used to deliver agents in the past, but have necessitated the use of complicated multi-chambered moving-barrier apparati such as disclosed in *Austral. J. Exp. Biol.* Vol. 30, pp. 415—420 (1955). The device of this reference has three compartments. One is filled with water and is separated from a second by a semipermeable membrane. The second compartment contains a congo red solution. The congo red solution osmotically draws water from the first chamber through the membrane. As the volume of the second chamber increases it applies a pressure to the third chamber which contains agent and causes the agent to be discharged.

Another prior art attempt to provide an agent dispensing device is disclosed in United States Patent No. 3,604,417. The device disclosed in this patent requires a semipermeable membrane and an osmotically effective solute separated from a solution of the agent by a movable piston. The movable piston is driven by osmotic pressure and forces agent from the device. The need for a moving piston severely restricts the shape of the device and causes construction problems that have limited the use of the device. The prior art has not provided an osmotic delivery device simple of construction having no moving parts which will permit controlled sustained release of a wide range of active agents over prolonged periods of time.

It is a primary object of this invention to provide such an osmotic delivery device.

The present invention therefore provides a simple osmotic delivery device. This device is comprised of a wall surrounding and containing an osmotically effective solute comprising an active agent, the wall having a small passage-way communicating with the active agent-comprising solute and the exterior of the device. The wall of the device is comprised in at least a part of a material that is semipermeable to external fluid common to the environment of use and essentially impermeable to the active agent. In use, the external fluid (usually water) permeates the semipermeable parts of the wall and dissolves a portion of the osmotically effective solute containing active agent enclosed within the wall. As more fluid permeates the wall, an osmotic pressure is developed which causes agent to be discharged through the small passageway. Optionally, a coating of material that erodes in certain environments is carried on the semipermeable membrane to moderate the rate of release, the coating permitting the area of semipermeable material exposed to vary. As long as

D3

these is undissolved osmotic solute inside the device, the solution of osmotically effective solute inside the device is maintained saturated and the area of the semipermeable membrane is constant, the rate at which dissolved agent is released from the device will remain constant, that is, there will be a rate of release which has a zero order time dependence.

In cases where the active agent is released in a particulate (such as micronized) form, the release rate of active agent may not perfectly parallel the release of the osmotic solute. By adjusting the ratio of active agent to osmotic solute, a constant rate release of agent can be obtained.

The features and advantages of this invention will become apparent from the following detailed description of the invention and from the following drawings wherein like reference numerals designate like parts.

Fig. 1 is a cut away view of a delivery device of the invention.

Fig. 2 is a top view of a device of the invention embodied as an ocular drug delivery device.

Fig. 3 is an enlarged cross-sectional view at 3—3 of the device of Fig. 2.

Fig. 4 is an exploded perspective of the device of Fig. 2.

Fig. 5 is a diagrammatic elevational view of a human eye with the device of Fig. 2 in operative position.

Fig. 6 is a cross-sectional front view of a uterine cavity showing a delivery device of the invention positioned therein.

Fig. 7 is a partial cross-sectional view of an osmotic anal drug delivery device of the invention.

Fig. 8 is a cross-sectional view of a device of the invention embodied as an osmotic oral dosage form.

Fig. 9 is a cross-sectional view of an embodiment of the invention having temporary erodible coatings over the semipermeable membranes to change the rate of agent release from the device.

Fig. 10 is a cross-sectional view of a device of the invention embodied as an osmotic oral drug dosage form with an erodible outer coating.

Figs. 11—14 are graphs illustrating the patterns of agent release obtainable with devices of the invention.

The present invention provides an osmotic device for the controlled and continuous delivery of an active agent to a liquid containing environment of use over a prolonged delivery period. This device comprises a wall formed at least partly of a semipermeable material, said wall being characterized by maintaining its integrity during the delivery period, and said material being permeable to the passage of the liquid in the environment of use and being substantially impermeable to the passage of the active agent, the wall surrounding and defining a compartment; said compartment containing an osmotically effective substance comprising the active agent and at least one predefined small passageway communicating with the compartment and with the exterior of the device for releasing active agent from the device.

According to a further feature of this invention, there is provided a process for production of an osmotic device for the controlled and continuous delivery of an active agent to a liquid containing environment of use over a prolonged delivery period characterized by:—

a) forming a core of an osmotically effective substance comprising an active agent,

b) enveloping the core in a semipermeable membrane material which maintains its integrity during the delivery period, is permeable to the inward passage of liquid from the environment of use, and is substantially impermeable to the passage of the active agent in the core and

c) forming at least one hole in the membrane as an outlet passageway for the active agent, the hole being sized so that the active agent is delivered substantially by osmotic pumping.

The novel osmotic delivery device of the invention is shown in Fig. 1 by the number 10. Delivery device 10 has body portion 11. Body portion 11 has a wall 14 surrounding a compartment 15 as shown by open section 13. Compartment 15 is a means for containing an active agent or an active agent-containing mixture (not shown). Neck 12 is attached to body 11 and can be integrally formed with body 11, or can be separately manufactured and then joined to body 11.

Wall 14 of delivery device 10 is comprised at least in a part of a semipermeable material. The semipermeable material of wall 14 has uniform properties across all

D3

its dimensions, that is, it is substantially imperforate and substantially homogeneous. In operation, when device 10 is placed in an external fluid environment, molecules of external fluid dissolve in and diffuse through the semipermeable material of wall 14. Then the external fluid contacts the active agent or agent-containing mixture. The agent or a non-active component of the mixture must be an osmotically effective solute and dissolve in the external fluid creating a fluid activity gradient across the semipermeable material of wall 14. This activity gradient causes further diffusion of solvent molecules into compartment 15 so that an osmotic pressure develops and solvent containing osmotic solute molecules (and active agent) is discharged from device 10 to environment 17 via passageway 16. The rate of agent discharge from device 10 will remain constant so long as undissolved osmotic solute remains within compartment 15.

In Figures 2, 3, 4, and 5 another typical device of the invention, device 10, is shown in various views. The description of this embodiment of the invention and its operation also applies to other embodiments. This device 10 is a bean-shaped ocular drug delivery device. As clearly shown in Fig. 4, device 10 has a hollow compartment enclosed by and defined by the laminated combination of outer walls 14 and 18 and inner wall 19. Wall 19 also defines a small passageway 16 from the inner compartment of hollow device 10 to the external ocular environment of use 17. The inner compartment (15 in Fig. 3) contains a composition at least in part soluble in the fluid of the external ocular environment and containing drug (20 in Fig. 3). At least a portion of the wall of device 10 enclosing inner compartment 15, i.e. walls 14, 18 and 19, is semipermeable, permitting fluid from the ocular environment (in this case water) to selectively permeate by diffusion into inner compartment 15.

Any or all of walls 14, 18 and 19 can be semipermeable as described. Those portions of the walls surrounding compartment 15 which are not semipermeable should be essentially impermeable to the fluids of the external ocular environment and the contents of compartment 15.

The materials of walls 14, 18 and 19 should be substantially insoluble in the ocular fluids during the term of drug release, non-allergenic and biologically inert. When the walls of device 10 are of insoluble material, it is necessary to remove the device after it has exhausted its drug supply. It is possible to eliminate this removal by using walls which remain intact throughout the term of drug release and biocrode to harmless endproducts only thereafter.

Enclosed in compartment 15 of device 10 is an osmotically effective composition comprising an ocular drug. To be osmotically effective, some component of the composition must be soluble in the fluid of the external environment which permeates the walls of device 10 (shown as 21 in Fig. 3). In the ocular device of Figs. 2—5 the permeable fluid is water from tears, so some component of the composition must be water soluble. This solubility is needed to permit the composition to function as an osmotically effective solute, i.e. to create a water activity gradient across the semipermeable walls and generate an osmotic pressure inside device 10. Permeable-fluid-soluble drugs alone can make up the composition in compartment 15. Insoluble drugs may be used admixed with added osmotically effective solute.

In use, ocular device 10 of Figs. 2—5 is placed in the cul-de-sac of the eye as shown in Fig. 5. In Fig. 5 device 10 is positioned in immediate contact with eyeball 33 for osmotically administering drug to eye 29. Eye 29 is comprised of eyelids 30 and 31, eyelashes 32 and 36, and eyeball 33 covered for the greater part of its posterior area by a sclera 34 and at its central area by a cornea 35. Eyelids 30 and 31 are lined with an epithelial membrane or palpebral conjunctiva, not shown. Sclera 34 is covered with the bulbar conjunctiva. The portion of the palpebral conjunctiva which lines upper eyelid 30 and the underlying portion of the bulbar conjunctiva defines an upper cul-de-sac, not seen in Fig. 5 while that portion of the palpebral conjunctiva which lines lower eyelid 31 and the underlying portion of the bulbar conjunctiva defines a lower cul-de-sac, shown by dashed line 38. Device 10 of Figs. 2—4 may be inserted in either cul-de-sac and is depicted in Fig. 5 in dashed lines in operative position.

The osmotic device of this invention can be used for release of a wide variety of active agents. The term "active agents" as used in this specification and the accompanying claims include those compounds or compositions of matter which, when dispersed, produce a predetermined beneficial and useful result in fluid-containing environments of use. Active agents include for example, pesticides, herbicides, germicides, biocides, algicides, rodenticides, fungicides, insecticides, anti-oxidants, plant growth promotors and inhibitors, preservatives, surfactants, disinfectants, catalysts, fermentation agents, nutrients, drugs, plant minerals, sex sterilants, plant hormones,

D3

air purifiers, and micro-organism attenuators. The dispensing device of this invention can assume appropriate shapes and sizes for releasing these agents in desired fluid containing environments; such as body cavities, streams, aquariums, field, and reservoirs.

In the great majority of these environments, such as in agricultural or physiological environments, water is present and is the fluid of choice for permeating the semipermeable walls of the device. Thus the materials for preparing the semipermeable portions of the walls of the devices of the invention are materials which are permeable to water but substantially impermeable to solutes. Typical materials for forming the wall include osmosis and reverse osmosis membranes such as unplasticized cellulose acetate, plasticized cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate, cellulose ethers, cellulose acetate propionate, poly(vinyl methyl) ether copolymers, cellulose acetate diethylaminoacetate, cellulose acetate octate, cellulose acetate laurate, methyl cellulose, cellulose acetate p-toluene sulfonate, triacetate of locust gum bean, cellulose acetate with acetylated hydroxyethyl cellulose, hydroxylated ethylene-vinylacetate, aromatic nitrogen-containing polymeric membranes that exhibit water permeability and essentially no solute passage, osmosis membranes made from polymeric epoxides, and osmosis membranes made from copolymers of an alkylene oxide and alkyl glycidyl ether.

Generally, materials having a fluid permeability of 0.01 to 10 cc/cm^2 hour or higher at atmospheric pressure against a saturated solution of the compartment contents at the temperature of use while simultaneously possessing a high degree of impermeability to the solute are useful for manufacturing semipermeable walls of the devices of the invention. Preferred materials have water sorptions of greater than five percent and less than thirty percent by weight at ambient temperatures. The compositions contained within and osmotically released from the devices of this invention contain a wide range of "active agent" as already noted. One class of active agents deliverable by the devices is drugs. The term "drug" broadly includes physiologically or pharmacologically active substances for producing a localized or systemic effect at the location of administration or at a site remote from the point of application.

Drugs that may be administered include inorganic and organic compounds, for example, drugs acting on the central nervous system such as hypnotics and sedatives, i.e., pentobarbital sodium and phenobarbital; psychic energizers such as isocarboxazid and nialamide; tranquilizers such as chloropromazine and promazine; anticonvulsants; muscle relaxants and anti-parkinson agents; antipyretics and anti-inflammatory agents such as aspirin; local anesthetics such as procaine; antispasmodics and antiulcer agents such as scopolamine; prostaglandins such as PGE_1, PGE_2, $PGF_{1\alpha}$, $PGF_{2\alpha}$, and PGA; anti-microbials such as penicillin; hormonal agents such as prednisolone; estrogenic steroids, for example, 17β-estradiol and thinyl estradiol; progestational steroids, such as for contraceptive purposes, for example 17α-hydroxy-progesterone acetate, 19-nor-progesterone, norethindrone and the like, sympathomimetic drugs; cardiovascular drugs; diuretics; antiparasitic agents; hypoglycemic drugs; and eye drugs such as pilocarpine base, pilocarpine hydrochloride, pilocarpine nitrate.

Various osmotically-effective solute additives including organic and inorganic compounds are advantageously added to the active agents when it is desired to release an active agent having limited solubility in the permeating fluid, i.e. water. The term "limited solubility" as used herein means that the agent has a solubility of about less than 1% by weight in the fluid. Useful osmotically-effective added solutes includes salts such as magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, calcium bicarbonate, sodium sulfate, calcium sulfate, potassium acid phosphate, and calcium lactate; compounds such as d-mannitol, urea, inositol, tartaric acid, raffinose, sucrose, glucose and α-d-lactose monohydrate.

By adding varying amounts of these solute additives to the limited solubility active agents, an increased water activity gradient across the semipermeable wall results with a concomitant increased unidirectional flow of fluid through the wall and agent discharge rate.

These added solutes may also be added to more soluble agents to adjust their rate of osmotic discharge. The solutes are conveniently used by mixing with the active

D3

agent, either before charging into the compartment or by self-mixing after charging into the compartment.

When the agent is soluble, it will usually be released as a saturated solution in the fluid osmotically permeating the walls.

When the agent is of limited solubility it may be desired to discharge it as a suspension in the flowing fluid. In this latter case, it is necessary that the agent be in particles small enough to pass through the discharge opening. Preferably these particles should be not greater than from 3/4 to 1/10 the size of the discharge passageway. Often it is desirable to promote suspension in the fluid by adding a protective colloid or dispersant to the agent solute. Exemplary colloids or dispersants include the water-soluble gums, carboxymethylcellulose, poly(vinyl alcohol), gelatin and non-toxic surface active agents such as glyceryl monostearate, lecithin and sorbitan monoleate.

The amount of active agent initially present in the device is generally non-limited and is an amount larger than or equal to the sum of the amount of agent that is necessary to osmotically operate the device plus the amount of agent which upon release from the device is effective for bringing about the agent's desired effect. Since the invention contemplates a variety of devices of various sizes and shapes for a variety of uses there is no critical upper limit on the amount of agent incorporated in the device. The lower limit will depend on osmotic activity, the span of the release of the product and the activity of the agent. Generally, the device will contain from 0.01% to 90% wt. or higher of an agent or a mixture of agent and solute. Typically, the device can be of such size and shape to release from 0.01 cc to 5 cc of product contained in the fluid per hour for several hours, days, months, or longer.

The expressions "passageway" and "passageway communicating with" define means for releasing the product from the device under the osmotic pumping rate of the device. The expression includes apertures, orifices, and porous elements through which the product can migrate. The expression also includes biocrodible materials that erode in the environment of use to produce a passageway.

The size of the passageway should be so that the rate of agent delivered,

$$\frac{Q_D}{t}$$

attributable to diffusion in the fluid present in the passageway is always less than the rate attributable to pumping of the entire contents of the device,

$$\frac{Q_P}{t}$$

through the passageway. Preferably

$$\frac{Q_D}{t}$$

is substantially less than

$$\frac{Q_P}{t}$$

such as 0.1 times

$$\frac{Q_P}{t}$$

In the devices of the invention where

$$\frac{Q_P}{t}$$

is greater than

$$\frac{Q_D}{t}$$

D3

the device is essentially an osmotic powered device. The rate of pumping from a device of the invention is given by the following equation:

$$\frac{Q_p}{t} = k\frac{A_m}{t_m} \times \text{osmotic pressure} \times \frac{\text{drug solubility}}{1 + \frac{\text{drug solubility}}{\text{drug density}}}$$

wherein A_m=area or membrane, t_m=thickness of membrane, and k is a permeability coefficient defined as

$$\frac{\text{cc of fluid}}{\text{hr cm}^2} \times \frac{\text{thickness of membrane}}{\text{osmotic pressure}}$$

To assure the desired osmotic mechanism, the maximum size of the passageway should be controlled by expression

$$\frac{A_s}{L} = \frac{1}{F}\frac{Q_p}{t} \times \frac{1}{DS}$$

wherein A_s is the cross sectional area of the passageway, L is the length of the passageway (for a device with a passageway through a membrane it corresponds to the thickness of the membrane), D is the diffusion coefficient of the active agent in the solution osmotically attracted into the device, S is drug solubility in g/cc and

$$F = \frac{Q_{p/t}}{Q_{s/t}}$$

(F should always have a value of at least 2 and preferably greater than 10, and such as from 10 to 1000).

The minimum size of the passageway is set to prevent generation of sufficient pressure to burst a wall of the compartment, i.e. to prevent ΔP rising too high. This minimum size can be determined, by the general equation

$$A_S = \left[\frac{L Q_p}{t} \times 8\pi \times \frac{\eta}{\Delta P}\right]^{1/2}$$

wherein A_s is the cross-sectional area of the passageway, η is the viscosity of the solution in the passageway, ΔP is hydrostatic pressure difference between the inside and the outside of the device, (preferably less than 20 atmospheres), L is the length of the passageway and $Q_{p/t}$ is the fluid flow rate from the device.

The devices of the invention are made with at least one passageway. The number of passageways may be varied so long as the cumulative dimensions meet the above limits.

While in Fig. 1 a generic osmotic device is shown and in Fig. 2 an ocular drug delivery device is shown, it is to be understood that the delivery devices of the invention can take a wide variety of shapes, sizes and forms for administering the wide range of active agents at controlled rates to different areas and environments as for example, the invention may take the form of prills, pills, tablets, rods, sheets, and grains for administering agents, such as bio-agents to environments such as fields; or it may, in drug delivery situations take the form of oral drug delivery devices such as tablets and pills, vaginal devices, implants, buccal devices, prostbesis, cervical rings, intrauterine devices of any geometrical shape that readily lends itself to intrauterine placement and ocular drug delivery devices of any convenient geometric shape for comfortable retention in the cul-de-sac of the eye.

In Fig. 6 device 10 is fashioned as an intrauterine device for osmotically administering an antifertility agent. Device 10, has an "H" configuration. It is adapted for placement within a uterine cavity and connecting the sides 23 and the fundus

D3

uteri 24 of uterus 25. A removal thread 26 is attached to the trailing end 27 of device 10. Device 10 is comprised of a wall 14 formed of a semipermeable membrane surrounding a product compartment 15. Passageway 16 communicates with compartment 15 in uterus 23. Compartment 15 contains an antifertility agent 20 that may be soluble in and exhibit an osmotic pressure gradient against uterine fluid that enters the compartment through semipermeable wall 14. The agent may also have limited solubility in the permeable fluid, in which case an osmotically effective solute that is soluble in uterine fluid and exhibits an osmotic pressure gradient against external uterine fluid will be admixed with it. Wall 14 lets uterine fluid or water therefrom permeate into chamber 15 at a rate controlled by its permeability. The fluid entering chamber 15 dissolves or picks up dispersed particles of agent 20. As further fluid enters chamber 15, this saturated solution or dispersion of agent is discharged to the uterus through passageway 16 at a rate that corresponds to the rate of fluid permeability through the membrane which is controlled by the osmotic attraction to the fluid as expressed by the osmotic pressure gradient across the wall.

Fig. 7 illustrates another dispensing device 10 of the invention. Device 10 is designed for administering a drug 20 within an anal canal, not shown. Device 10 is comprised of a wall of semipermeable film 14 shaped like an obelisk with a lead end 8 and a tailing end 9. Wall 14 surrounds a product compartment 15 defining a reservoir. The reservoir contains solid drug 20. Drug 20 is released from device 10 at a controlled rate over a prolonged period of time through passageway 16 which terminates at outlet 17. Wall 14 can be isotropic, or anisotropic. In this osmotic suppository, drug is released by the mechanism already described.

In Fig. 8 is a device 10 of the invention as shown. Device 10 is a dosage form for oral administration of medication. Device 10 has a wall 14 formed at least in part of a semipermeable material. Passageway 16 communicates with the exterior of the device and in response to osmotic action releases medication 20 to the exterior of the device. Device 10 can have more than one passageway.

The amount of osmotically effective substance present in the just described devices is initially in excess of the amount that can be dissolved in the fluid present in the interior of the device. The said substance may be the active agent *per se*, or the active agent admixed with an appropriate composition. Under this physical state, (when the drug is in excess), the device will osmotically operate to give essentially zero order rate of release. The rate of agent release can be varied if desired by covering at least a portion of the semipermeable material with a pattern rate controlling material.

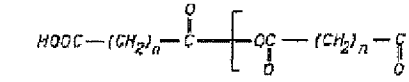
The pattern rate controlling material erodes in the environment and exposes varying amounts of semipermeable material. This causes the rate of fluid entry into the device and hence the rate of active agent discharge, to vary. The use of such pattern rate controlling coatings is depicted in Fig. 9 where a cross-section of a device 10 is shown. The device of Fig. 9 is similar to the device of Fig. 3 with the addition of the pattern rate coatings. Device 10 of Fig. 9 has walls 14, 18 and 19 which define an inner compartment 15. Located within compartment 15 is active agent 20 and liquid 21. Walls 14 and 18 are semipermeable and if uncovered would permit external liquid from the environment of use to permeate into compartment 15 and osmotically release agent 20 through a small passageway not shown. Walls 14 and 18 are covered by pattern rate controlling coatings 9. Coating 9 is formed of synthetic or naturally occurring materials which possess quick or slow erosion properties and are impermeable to the passage of external fluids. Coating 9 undergoes erosion in the environment by such processes as solubilization, hydrolysis or the like. Different areas of the semipermeable material may be coated with different pattern rate controlling coatings so that varying areas of semipermeable material are exposed with corresponding varying drug discharge rates.

The pattern rate coatings to be effective, are impermeable to the fluid which permeates the semipermeable walls. One class of suitable materials for pattern rate controlling materials most useful for oral dosage forms for drugs are the enteric coatings that give a predetermined release rate profile by resisting the action of stomach fluid to prevent water permeating through the wall, while disintegrating in the intestine to let fluid enter the device. The enteric coatings suitable for the present invention include those materials digestible by the enzymes in the intestinal tract and materials containing an ionizable polyacid, frequently a long-chain polymer with ionizable carboxyl groups, and the like. Typical materials for forming enteric coatings include keratin, keratin over sandaracolu, ternary copolymers of styrene, methacrylic acid with butyl half-ester of maleic acid, and the like. Typical enteric coatings

D3

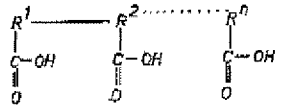
are discussed in *Remington's Pharmaceutical Sciences*, Thirteenth Ed., pages 604 to 605, 1965 Mach Publishing Co., Eaton, Penna.

The coating 9 carried on semipermeable wall 14, can also be made of a time release profile material that gradually erodes at a predetermined rate in environmental fluids thus exposing the semipermeable wall to the surrounding fluid. By adjusting the thickness of the coating any desired release profile can be programmed. Exemplary materials include those materials which slowly dissolve in fluids, and coating materials that hydrolize in body fluids, for example, the polymeric essentially linear, dibasic acid anhydrides of the formula



Other coatings include polyanhydride polymers of sebacic and azelaic acid, and polyhydroxyacetic acids.

Coating 9 can also comprise a hydrophobic poly(carboxylic acid) having an average of one ionizable hydrogen for each 8 to 22 carbon atoms. These polyacid coatings erode by a process of carboxylic hydrogen ionization. This erosion extends over a prolonged period of time and exposes the semipermeable wall over a corresponding prolonged period of time. Exemplary poly(carboxylic acids) materials useful as coatings are the hydrophobic polyacids which are represented by the general formula:



wherein the R's are organic radicals independently selected to provide, on average, from 8 to 22 total carbon atoms for each carboxylic hydrogen. Variations of this ratio within this range can vary the erosion rates prepared from these polymeric acids. Organic radicals represented by R^1, R^2, . . . R^n may be selected from hydrocarbon radicals and heterostom containing organic radicals. Suitable hetero atoms for employment in R^1, R^2, . . . R^n include oxygen, nitrogen, sulfur, and phosphorus as well as other hetero atoms.

One group of coating materials used to coat the osmotic dispensing device of the invention comprise hydrophobic polymers of an acid selected from acrylic acid, lower alkyl acrylic acids of from 4 to 6 carbon atoms per monomeric unit, and maleic acid; either alone or copolymerized with up to about 2 moles per mole of acid of an olefinically unsaturated compound such as ethylene or an alkyl vinyl ether in which the alkyl contains 1—4 carbon atoms, wherein from about 20% to 90% of the acid groups have been esterified with an alkanol of from 1 to about 10 carbon atoms and wherein the ratio of total carbon atoms to acidic carboxylic hydrogens is in the range of from about 9:1 to about 20:1. Also, suitable coatings include the hydrophobic partially esterified copolymers of acrylic acid, methacrylic acid or maleic acid with from 0.2 to 1.5 moles, per mole of acid of ethylene or an alkyl vinyl ether in which the alkyl contains 1 to 4 carbon atoms said copolymer having from about 35% to about 70% of its carboxylic groups esterified with lower alkanol of from about 3 to about 10 carbon atoms, said copolymers having a carbon to acidic carboxylic hydrogen ratio of from about 10:1 to about 15:1. The coatings further include hydrophobic copolymers of maleic acid with about one mole, per mole of maleic acid, of ethylene or methyl vinyl ether, said copolymer having about half of its total carboxyl groups esterified with a lower monoalkanol of from 4 to 8 carbon atoms, wherein the carbon to acidic carboxylic hydrogen ratio has a value of from about 10:1 to about 14:1. Other time delay materials include fatty acids having 10 to 22 carbons, fatty alcohols having from 14 to 30 carbons, the esters of mono-, di-, or triglyceryl esters formed from fatty acids having 10 to 22 carbon atoms and silicone and substituted silicone derivatives.

These rate pattern coatings are especially effective with osmotic oral dosage forms for drugs such as device 10 of Fig. 10.

A device for releasing medication at a zero order rate to a preselected environ-

D3

ment; device 10 is suitably adapted for the oral administration of a medication. Device 10 is comprised of a wall 14 formed either fully or in at least a part of a semipermeable film forming membrane that surrounds medication. A coating 9 of constant or varying thickness that erodes or undergoes dissolution in the gastrointestinal tract is coated onto semipermeable wall 14. Coating 9 can be an enteric coat which is not disintegrated in the stomach and yet is readily available for dissolution in the upper intestinal tract. It also can be a material that gradually and continually erodes or undergoes dissolution as the device travels through the gastrointestinal tract. A passageway 16 releases medication to the exterior of the device. Device 10 has at least one passageway and it can have additional passageways to release the same amount of drug or more drug at various osmotic pumping rates to the host or the environment.

The invention will be further described by the following examples.

EXAMPLE 1

An osmotic drug delivery device is manufactured substantially in accord with Figs. 2, 3 and 4. It has an ellipse shape and is comprised of two outer semipermeable walls (14 and 18 in the Figures) each fused to an inner middle wall (19) having a center area defining a compartment for containing a drug. A drug release passageway (16) passes from the inner compartment to the exterior of the device.

First, material for the two semipermeable walls is formed by thoroughly mixing 1 part polyurethane ether (Estane® 5714 of B. F. Goodrich Co.) with 3 parts tetrahydrofuran and drawing a 0.25 mm film of the mixture on silicone release paper. The film is air-dried at room temperature to yield a material about 0.06 mm thick. Two semipermeable elliptical walls for the device, each about 16 mm × 6.75 mm, are cut from the film. Next, a middle wall material is prepared by mixing 20 parts ethylene vinylacetate, 80 parts methylene chloride and 9.1 parts blue lake and casting a film which upon drying is 0.10 mm thick. This film is cut into a 0.5 mm wide hollow 16 mm × 6.75 mm ellipse. The middle wall is laminated to one of the semipermeable walls with a vacuum laminator.

A water soluble (0.25 g/cc) osmotically effective drug, pilocarpine nitrate, is dispersed in ethylene/vinylacetate copolymer, the weight ratio of the drug to the copolymer being 80:20 and placed into the compartment of the middle wall. The copolymer is not a solvent, but acts as a film former to facilitate handling of the liquid drug. A porous silk suture is laid over the middle ring and the third wall is laminated over the suture and the middle ring.

When this device is placed in a human eye, water from tear fluid is immediately osmotically drawn through the semipermeable membrane into the central compartment of the device where it dissolves the drug. As more water is drawn in, an osmotic pressure is rapidly developed which dispenses the drug out along the porous silk suture which effectively defines a passageway from the central compartment to the exterior of the device. The rate of pilocarpine nitrate release from this device is a controlled constant 30 μg/hour.

EXAMPLE 2

An osmotic delivery device for osmotically releasing the active agent, potassium chloride, is prepared. (Potassium chloride is useful as a drug but also finds use as an ice and snow removal agent and as an ionic strength adjusting agent.) Potassium chloride crystals and a binder are compression molded into 500 mg/9.5 mm diameter tablets. The tablets are coated with cellulose acetate (Eastman Kodak E-320) using a Wurster air suspension apparatus and a 5% solution of polymer in dioxane. The thickness of the coating is about 0.25 mm. A passageway is cut to the potassium chloride core of each coated tablet by mechanical drilling or laser drilling the outer coatings. The diameters of the passageways range from 0.10 mm to 0.27 mm.

When the devices are placed in an aqueous test environment they imbibe water through their semipermeable outer coatings. This water dissolves active agent. The solution of active agent is discharged under osmotic pressure at a rate of 26 mg ± 5% of KCl discharged per hour. This rate remains constant over a prolonged period as shown in Fig. 11. The rate is not dependent on the size of the passageway over the range tested. When, in further tests, the passageway size is lowered to 0.0025 mm or less or increased to 0.50 mm or larger, osmotic release results, but often at rates which vary proportionally to passageway size.

EXAMPLE 3

Devices are made according to Example 2. The devices are weighed and color

D 3

coded. A series of eight coded devices are administered to two dogs at regular time intervals. 12 hours after the first devices are administered, the dogs are sacrificed, and the devices are recovered, rinsed, dried and weighed. The weight of KCl released from each device is plotted in Fig. 12. The average rate of KCl release is 24.3 mg/hour, a value in agreement with the value determined in Example 2.

EXAMPLE 4

700 mg portions of sodium phenobarbital are compressed into capsule-shaped cores. The cores are impaled on 0.4 mm diameter wires and then dip-coated in a solution of cellulose acetate (Eastman Kodak E-376) in dioxane and dried. The dry cellulose acetate coating is about 0.28 mm thick. The wires are removed to give passageways having a 0.4 mm diameter. These devices release phenobarbital by an osmotic mechanism at a constant rate. When these devices are placed in simulated gastric juice for two hours and then in simulated intestinal juice (as described in *The United States Pharmacopoeia*, Eighteenth Revision, pages 1026 and 1027, 1970) release rates independent of pH are observed, as shown in Fig. 13.

EXAMPLE 5

The device preparation of Example 1 is repeated. The devices are then subjected to an additional processing step. The semipermeable walls are coated with a water-impermeable release rate profile coating of hydrophobic polymer.

The profile coating is the n-pentanol half ester of ethylene-maleic anhydride copolymer.

The copolymer is prepared as follows: 12.6 grams (0.10 equivalents) of ethylene-maleic anhydride copolymer (Monsanto EMA, Grade 31) is stirred with 50 ml (0.6 moles) of n-pentyl alcohol at 120—125°C for 7 hours. The solution is cooled and methylene chloride is added to precipitate the product (total vol. 3 l). The precipitate is separated and dissolved in 75 ml acetone. Acetone is removed to yield the polymer product which upon analysis is found to be the pentyl half ester of the acid form of the original anhydride copolymer.

This polymer is dissolved in a minimum amount of acetone and spread on the semipermeable walls of the devices with a doctor blade and permitted to dry. When the coated product is placed in a human eye, initially there is no release of drug from the inner compartment since the water impermeable release rate profile coating prevents the passage of water through the semipermeable walls and thus no osmotic pressure or osmotic pumping of the drug results. The profile coating is erodible, however, so that after an initial period, the semipermeable walls are exposed to water and controlled prolonged osmotic delivery of the drug begins.

EXAMPLE 6

A number of the cellulose acetate-coated devices prepared in Example 2 are given an additional outer coating. This coating is an enteric coating that resists the acidity of the stomach and prevents any fluid entering the compartment and release of drug from the device but which disintegrates in the alkalinity of the intestine and permits osmotic drug release. Useful enteric coatings that can be applied include keratin, calcium alginate and shellac. The release profile for this device is first a non-release state in the stomach with a release state in the intestine after disintegration of the coating as illustrated in Fig. 14.

EXAMPLE 7

An osmotic delivery device for example in accord with Example 1 having two semipermeable membranes is coated on only one membrane with a drug release rate profile enteric coating (shellac-n-butyl stearate mixture). When this device is taken orally and passes into the stomach, drug is osmotically released at a constant rate. When the device passes into the intestine, the enteric coating disintegrates exposing additional semipermeable membrane and the rate of osmotic release increases proportionally to a new constant rate.

WHAT WE CLAIM IS:—

1. An osmotic device for the controlled and continuous delivery of an active agent to a liquid containing environment of use over a prolonged delivery period, said device comprising:

a wall formed at least partly of a semipermeable material, said wall being characterized by maintaining its integrity during the delivery period, and said material being permeable to the passage of the liquid in the environment of use and being

D3

substantially impermeable to the passage of the active agent, the wall surrounding and defining a compartment;

said compartment containing an osmotically effective substance comprising the active agent;

and at least one predefined small passageway communicating with the compartment and with the exterior of the device for releasing active agent from the device.

2. The osmotic device according to claim 1 wherein the agent is soluble in the liquid of the environment.

3. The osmotic device according to claim 1 wherein the osmotically effective substance comprises the active agent mixed with an organic or inorganic solute that exhibits an osmotic pressure gradient against the liquid of the environment.

4. The osmotic device according to claim 1 wherein the liquid is water.

5. The osmotic device according to claim 1 wherein said device has only a single passageway.

6. The osmotic device according to claim 1 wherein the osmotically effective substance is present in the compartment in a proportion in excess of its solubility in the liquid.

7. The osmotic device according to claim 1 wherein the active agent is a plant nutrient, herbicide, pesticide, insecticide, germicide, fungicide or algicide.

8. The osmotic device according to claim 1 wherein the active agent is a drug.

9. The osmotic device according to claim 8 wherein the device is adapted and structured as an oral dosage form for administration of a drug to the gastrointestinal tract.

10. The osmotic device according to claim 8 wherein the device is an intrauterine device adapted for the release of a drug to the uterus.

11. The osmotic device according to claim 8 wherein the device is an ocular device adapted for insertion into the cul-de-sac of the eye.

12. The osmotic device according to claim 1 additionally comprising a release rate profile coating covering at least a part of the semipermeable material.

13. The osmotic device according to claim 8 additionally comprising a release rate profile coating covering at least a part of the semipermeable material.

14. The osmotic device in oral dosage form according to claim 9 additionally comprising a release rate profile enteric coating covering at least a part of the semipermeable material.

15. The osmotic device according to claim 1 wherein the semipermeable material comprises cellulose acetate.

16. The osmotic device according to claim 1 wherein the maximum size of the passageway is controlled by the equation:

$$\frac{A_s}{L} = \frac{1}{F} \frac{Q_p}{t} \times \frac{1}{DS}$$

in which A_s is the cross sectional area of the passageway, L is the passageway length, D is the diffusion coefficient of the active agent in the solution formed in the compartment, S is solubility in g/cc, F is at least 2 and

$$\frac{Q_p}{t}$$

is the pumping rate of the entire contents of the device and the minimum size of the passageway is controlled by the equation

$$A_s = \left[\frac{L Q_p}{t} \times 8\pi \times \frac{\eta}{\Delta P} \right]^{1/2}$$

where A_s, L and

$$\frac{Q_p}{t}$$

are as defined above, η is the viscosity of the solution in the passageway and ΔP is less than 20 atmospheres.

D3

17. The osmotic device of claim 16 wherein F is greater than 10.

18. A process for production of an osmotic device for the controlled and continuous delivery of an active agent to a liquid containing environment of use over a prolonged delivery period characterized by:

a) forming a core of an osmotically effective substance comprising an active agent,

b) enveloping the core in a semipermeable membrane material which maintains its integrity during the delivery period, is permeable to the inward passage of liquid from the environment of use, and is substantially impermeable to the passage of the active agent in the core, and

c) forming at least one hole in the membrane as an outlet passageway for the active agent, the hole being sized so that the active agent is delivered substantially by osmotic pumping.

19. A process according to claim 18 wherein the agent is soluble in the liquid of the environment of use.

20. A process according to claim 18 wherein the osmotically effective substance comprises the active agent mixed with an organic or inorganic solute that exhibits an osmotic pressure gradient against the liquid of the environment of use.

21. A process according to any of claims 18 to 20 wherein the liquid of the environment of use is water.

22. A process according to any of claims 18 to 21 wherein the device has only a single passageway.

23. A process according to any of claims 18 to 22 wherein the active agent is a plant nutrient, herbicide, pesticide, insecticide, germicide, fungicide, or algicide.

24. A process according to any of claims 18 to 22 wherein the active agent is a drug.

25. A process according to claim 24 wherein the device is adapted and structured as an oral dosage form for administration of a drug to the gastrointestinal tract.

26. A process according to claim 24 wherein the device is an intrauterine device adapted for the release of a drug to the uterus.

27. A process according to claim 24 wherein the device is an ocular device adapted for insertion into the cul-de-sac of the eye.

28. A process according to any of claims 18 to 27 wherein the device additionally comprises a release rate profile coating covering at least a part of the semipermeable membrane.

29. A process according to any of claims 18 to 27 wherein the semipermeable membrane material is cellulose acetate.

30. An osmotic device substantially as herein described with reference to and as illustrated in Figures 1 to 3 of the accompanying drawings.

31. A process according to claim 28 wherein the semipermeable membrane material is cellulose acetate.

32. An osmotic device substantially as herein described with reference to and as illustrated in Figures 9 and 10 of the accompanying drawings.

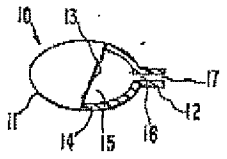
For the Applicants:—
F. J. CLEVELAND & COMPANY,
Chartered Patent Agents,
40—43, Chancery Lane,
London W.C.2.

Printed for Her Majesty's Stationary Office, by the Courier Press, Leamington Spa, 1975.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

D3

1415210 COMPLETE SPECIFICATION
5 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 1

FIG.1



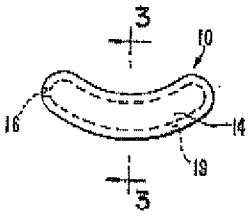


FIG.2

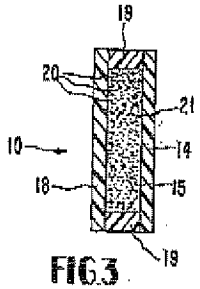
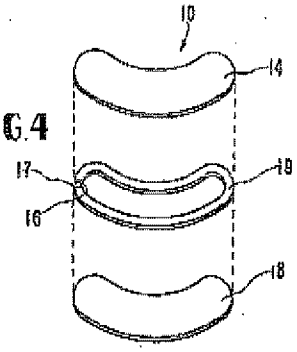


FIG.3

FIG.4



D3

1415210 COMPLETE SPECIFICATION
5 SHEETS This drawing is a reproduction of the Original on a reduced scale
Sheet 2

FIG.5

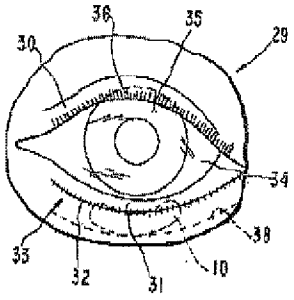
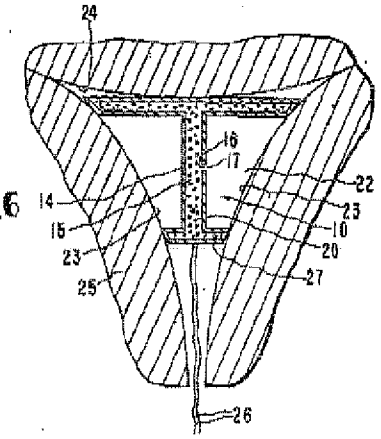


FIG.6



D3

1415210 COMPLETE SPECIFICATION
5 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 3

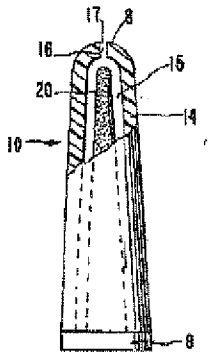


FIG.7

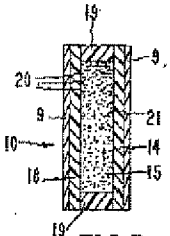


FIG.9

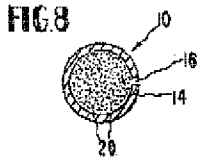


FIG.8

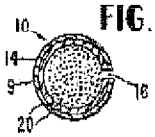


FIG.10

D3

1415210 COMPLETE SPECIFICATION
5 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 4

FIG.11

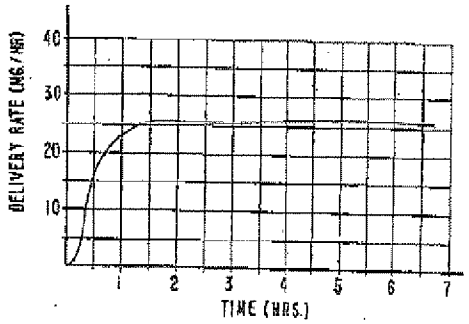
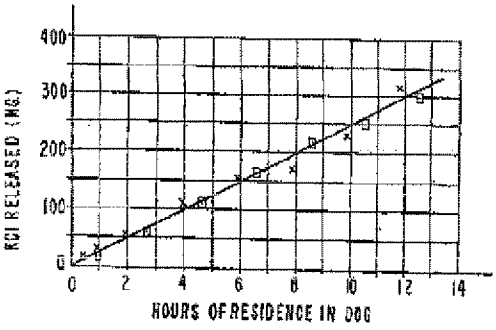


FIG.12



03

1415210 COMPLETE SPECIFICATION
5 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 5

FIG.13

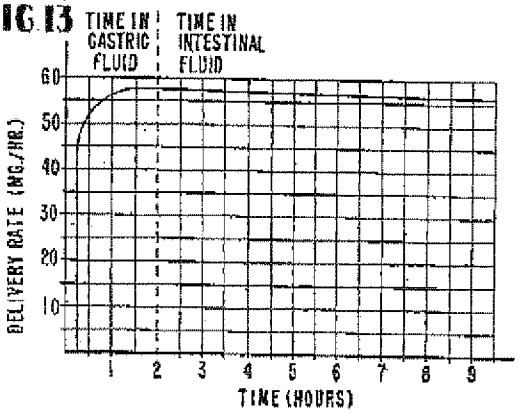


FIG.14